REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claims 37-39 and 42-68 are canceled without prejudice to or disclaimer of the subject matter therein. New claims 69-107 are added, as discussed in more detail below.

II. The Amendments to the Claims

Claims 69-107 are added to more clearly recite the invention and address the claim objections and indefiniteness rejections. Claims 69-79 are directed to a human IGFBP-2 molecule able to bind IGF-I or IGF-II with high affinity wherein a lysine in at least one of positions 180, 181, 227, 234 and 237 has been replaced with a neutral or acidic amino acid. These claims roughly correspond to previous claims 67-68, 42-49 and 51. Claim 80 is drawn to a human IGFBP-2 molecule able to bind IGF-I or IGF-II with high affinity wherein amino acids 114-170 have been deleted. This claim roughly corresponds to previous claim 50. Claims 81-96 are directed to methods of reducing IGF-mediated proliferation of cancerous cells using the human IGFBP-2 molecules recited in the previous claims. These claims roughly correspond to previous claims 37-39 and 58-66. Claims 97-107 are drawn to isolated nucleic acid molecules encoding the human IGFBP-2 molecules of the invention and roughly correspond to previous claims 52-57.

Support for the new claims may be found throughout the specification as filed, including at page 5, lines 18-20 (for replacement with a neutral or acidic amino acid), page 6, line 25 to page 7, line 9 (for specific replacements), page 16, line 15 to page 17, line 23 (for specific replacements and deletions), and page 20, lines 3-11 (for specific replacements and deletions). Because these amendments do not introduce any new matter, their entry is respectfully requested.

III. The Objections to the Claims

The Office Action, at page 2, objects to claims 67-68 because of formal matters. In view of the foregoing amendments, these objections are now moot. Withdrawal thereof is therefore respectfully requested.

IV. The Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office Action, at page 3, rejects claims 37-39 and 42-68 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Office Action alleges that the phrase "able to effect binding of" and the phrase "on contact with an extracellular matrix (ECM)" lack clarity. Applicant respectfully traverses. Nevertheless, solely to advance prosecution, and without acquiescing to the merits of the rejections, the foregoing replaces the phrase "effect binding of" with the verb "bind," as suggested by the Office Action, and does not use the phrase "on contact with an extracellular matrix (ECM)." Accordingly, these rejections are moot, and their withdrawal is respectfully requested.

V. The Rejections Under 35 U.S.C. § 112, First Paragraph

A. Scope of Enablement

1. The Rejection of Claims 42-47 and 67-68

The Office Action, at pages 3-7, rejects claims 42-47 and 67-68 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not reasonably provide enablement for the full scope of the molecules recited in the claims. Specifically, the Office Action alleges that the phrase "having an alteration" and the phrase "comprising a deletion" are infinitely broad, as there is no positive recitation of what structures must be present in order to have the recited functions. Applicant respectfully traverses this ground of rejection, in as much as it may be applied to the instant claims.

The instant claims do not contain the phrases "having an alteration" and "comprising a deletion," that the Examiner found objectionable. Instead, the claims recite human IGFBP-2 wherein a lysine in at least one of positions 180, 181, 227, 234 and 237 has been replaced with a neutral or acidic amino acid and/or wherein amino acids 114-170 have been deleted. Thus, the instant claims positively recite the claimed molecules, and this rejection is moot. Its withdrawal is therefore respectfully requested.

2. The Rejection of Claims 37-39 and 58-66

The Office Action, at pages 7-11, rejects claims 37-39 and 58-66 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not reasonably provide enablement for the full scope of the methods recited in the claims. Applicant respectfully traverses this ground of rejection, in as much as it may be applied to the instant claims..

As noted in MPEP § 2164.01, "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." Examples are not required for enablement. *See* MPEP § 2164.02. Moreover, as explained in the MPEP, a claimed genus can be enabled by "representative examples together with a statement applicable to the genus as a whole," as long as "one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation." MPEP § 2164.02. In the current application, Applicant has sufficiently disclosed the invention to enable the person skilled in the art to make and/or use the invention according to the MPEP guidelines.

The specification teaches that human IGFBP-2 molecules wherein a lysine in at least one of positions 180, 181, 227, 234 and 237 has been replaced with a neutral or acidic amino acid is useful for reducing IGF mediated proliferation of cancerous cells. While not wanting to be

bound by any theory, the specification explains that such human IGFBP-2 molecules exhibit inhibited release of IGF-I and IGF-II, for example, due to reduced binding to the extracellular matrix (ECM), because of the one or more amino acid replacements in ECM binding sites, such as the ECM binding site spanning residues 179-184 and the ECM binding site spanning residues 227-244. *See, e.g.,* specification at pages 3-6. These generic teachings are supported by specific data showing, for example, that human IGFBP-2 molecules with the replacements K180A and K181A or K234A exhibit reduced ECM binding compared to IGFBP-2. *See, e.g.,* specification at page 23, lines 6-12 & Fig. 8.

The Examiner appears to acknowledge enablement of embodiments where the lysines at both of positions 180 and 181 have been replaced with alanine, or where one of the lysines at positions 227, 234 or 237 have been replaced. While these embodiments are the subject of the working examples, the scope of the invention is not so limited. Indeed, as shown above, the specification provides ample teachings to enable other embodiments within the scope of the claims, including embodiments where only one of the lysines at positions 180 and 181 have been replaced, because, for example, such a replacement modifies an ECM binding site and is reasonably expected to result in reduced ECM binding and inhibited release of IGF-I and IGF-II.

The Examiner appears to acknowledge enablement of embodiments where amino acids 114-170 have been deleted. Indeed, the specification teaches that human IGFBP-2 wherein amino acids 114-170 have been deleted is useful for reducing IGF mediated proliferation of cancerous cells. While not wanting to be bound by any theory, the specification explains that human IGFBP-2 wherein amino acids 114-170 have been deleted exhibits inhibited release of IGF-I and IGF-II, for example, due to resistance to proteolysis. *See, e.g.,* specification at pages 3 & 7-8. These generic teachings are supported by specific data showing, for example, that human IGFBP-2 with the deletion 114-170 reduced proliferation of HT-29 colorectal cancer cells. *See,* e.g., specification at 23-24 & Fig. 6. Adenocarcinoma HT29 cells are human intestinal epithelial cells which produce the secretory component of Immunoglobulin A (IgA), and carcinoembryonic

antigen (CEA). These cells are routinely used in TNF studies as an assay system and as a model of colorectal cancer. *See, e.g.,* Wilson, CA and Browning, JL., *Cell Death and Differentiation 9*: 1321-33 (2002), attached as Exhibit A. Thus, data showing the effect of IGFBP-2 molecules of the present invention on HT-29 cell proliferation demonstrate the efficacy of the claimed invention in inhibiting proliferation of cancer cells.

In summary, the specification provides ample evidence that the skilled artisan could practice the full scope of the pending claims without an undue amount of experimentation. Accordingly, MPEP 2164.02 is satisfied, and this enablement rejection should be withdrawn

B. Written Description

The Office Action, at pages 11-13, rejects claims 42-57 and 67-68 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. According to the Office Action, while the specification discloses the specific mutations in the IGFBP-2 molecule, it allegedly fails to identify the remaining regions in the molecule that must be conserved. Applicant respectfully traverses this ground of rejection, in as much as it may be applied to the instant claims.

The Federal Circuit has recently clarified the law regarding written description in *Faulkner-Gunter Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006), a decision that is binding on the Patent Office. The court explains that the specification is written for a person skilled in the art and so it is not necessary to spell out every detail of the invention, only enough as is required to convince a person of skill in the art that the inventor possessed the invention and to enable the person to make and use the invention without undue experimentation. *Id.*

Neither the specification nor the claims need to recite the entire amino acid sequences of the claimed molecules in order to satisfy § 112. The instant claims recite human IGFBP-2 molecules having specific amino acid modifications, *e.g.*, specific replacements and/or deletions.

Human IGFBP-2 is known, and the specification sets forth relevant portions of the amino acid sequences of several embodiments. *See, e.g.*, specification at pages 6-7. While the specification does not set forth the amino acid sequence of each embodiment, it provides sufficient examples and information to plainly convey to the skilled artisan that Applicant possessed the full scope of the invention at the time of filing.

Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

CONCLUSION

Applicant submits that the application is in condition for allowance, and an early notice to that effect is earnestly solicited. Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned directly.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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